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# Pediatric Anesthesia

**A novel isotonic balanced electrolyte solution with 1% glucose for perioperative fluid management in children- an animal experimental pre- authorisation study**

**Running title: A novel balanced electrolyte solution**

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19 A novel isotonic balanced electrolyte solution with 1% glucose for perioperative  
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21 fluid management in children- an animal experimental pre- authorisation study  
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59 Running title: A novel balanced electrolyte solution  
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**Abstract**

*Background:* The recommendations for perioperative maintenance fluid in children have been adapted from hypotonic to isotonic electrolyte solutions with lower glucose concentrations (1-2.5% instead of 5%) in order to avoid hyponatraemia or hyperglycaemia.

*Objective:* The objective of this prospective animal study was to determine the margin of safety of a novel isotonic balanced electrolyte solution with 1% glucose (BS-G1) in comparison to normal saline with 1% glucose (NS-G1) in case of accidental hyperhydration with a focus on acid- base- electrolyte balance, glucose concentration, osmolality and intracranial pressure in piglets.

*Methods:* Ten piglets (bodyweight  $11.8 \pm 1.8\text{kg}$ ) were randomly assigned to receive either  $100\text{ ml}\cdot\text{kg}^{-1}$  of BS-G1 or NS-G1 within one hour. Before, during and after fluid administration electrolytes, lactate, haemoglobin, haematocrit, glucose, osmolality and acid-base parameters were measured.

*Results:* Unlike BS-G1, administration of NS-G1 produced mild hyperchloraemic acidosis (base excess BS-G1 vs. NS-G1, baseline  $1.9 \pm 1.7$  vs.  $2.9 \pm 0.9\text{ mmol}\cdot\text{l}^{-1}$ , study end  $0.2 \pm 1.7$  vs.  $-2.7 \pm 0.5\text{ mmol}\cdot\text{l}^{-1}$ ,  $p < 0.05$ , chloride BS-G1 vs. NS-G1 baseline  $102.4 \pm 3.4$  vs.  $102.0 \pm 0.7\text{ mmol}\cdot\text{l}^{-1}$ , study end  $103.4 \pm 1.8$  vs.  $109.0 \pm 1.4\text{ mmol}\cdot\text{l}^{-1}$   $p < 0.05$ ).

The addition of 1% glucose led to moderate hyperglycaemia ( $p < 0.05$ ) with a concomitant increase in serum osmolality in both groups ( $p < 0.05$ ).

*Conclusion:* Both solutions showed a wide margin of safety in the case of accidental hyperhydration with less acid-base-electrolyte changes when using BS-G1. This novel solution could therefore enhance patient's safety within the scope of perioperative volume management.

**Keywords:** balanced electrolyte solution, normal saline, children, margin of safety, acid-base, fluid management

## Introduction

Maintenance fluid therapy in children has been based for half a century on Holiday and Segar's recommendations suggesting the use of hypotonic fluids with 5% glucose added (1). After several reports of serious hyponatraemia or hyperglycaemia (2, 3), guidelines of several associations of paediatric anaesthesiologists now recommend the perioperative use of isotonic electrolyte solutions, i.e. normal saline or balanced electrolyte solutions with or without 1-2.5% glucose in order to avoid perioperative electrolyte and glucose imbalances (4, 5). Unfortunately these solutions were not commercially available on the German market (6, 7). Therefore in 2005, the association of German paediatric anaesthesiologists filed an application for approval of a balanced electrolyte solution with 1% glucose (BS-G1) with the German regulatory agency. In October 2009, this solution achieved a national approval and was introduced on the German market. In order to determine the margin of safety of BS-G1 in comparison to normal saline with 1% glucose (NS-G1) in case of accidental hyperhydration, we conducted a prospective animal experimental pre-authorisation study with focus on acid- base- electrolyte balance, glucose concentrations, serum osmolality and intracranial pressure.

We formulated the hypothesis that BS-G1 has less influence on the acid- base- electrolyte balance, when compared to NS-G1, while the other outcome parameters will not differ significantly between the groups.

## Material and Methods

After approval of the study by the local animal experimentation committee, ten female German landrace piglets, four weeks of age, were included in the study. After a water- only overnight fast, they received intramuscular premedication with azaperone and atropine. The piglets were then anaesthetised with intravenous propofol and fentanyl, orotracheally intubated and mechanically ventilated with 1.5% isoflurane in oxygen/air ( $F_i O_2$  0.5). The tidal volume was adjusted to maintain an end-tidal carbon dioxide tension of 40mmHg. All

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3 animals received  $20\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  fentanyl and  $0.5\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  rocuronium during the surgical  
4  
5 interventions. Body temperature was maintained by using an infrared lamp (LP1, Lister,  
6  
7 Germany) and a circulating water mattress (HICO Aquatherm 650, Hirtz, Cologne,  
8  
9 Germany). Heart rate, body temperature, and end-tidal carbon dioxide were measured using a  
10  
11 patient monitoring system (Cardiocap 5, Datex-Ohmeda, Freiburg, Germany). Using standard  
12  
13 cut down techniques, 5 F percutaneous sheath introducer sets (Arrow, Reading, USA) were  
14  
15 inserted in the right jugular vein and the right common carotid artery. Through the venous  
16  
17 introducer set, a 4 F two-lumen central venous catheter (Arrow, Reading, USA) was placed in  
18  
19 the superior vena cava for central venous pressure (CVP) recording. Additionally, a 20-G  
20  
21 cannula was placed in the right saphenous vein for fluid administration. Arterial pressure and  
22  
23 CVP were recorded from a calibrated pressure transducer. Thereafter all animals underwent  
24  
25 burr hole craniotomy (9mm) 1cm paramedian to the sagittal suture over the right cortex in  
26  
27 order to fix a 1.65mm precision pressure catheter (Neurovent P, Raumedic, Helmbrechts,  
28  
29 Germany) for intracranial pressure (ICP) measurements. Continuous ICP was monitored by  
30  
31 transduction of the cortex tissue with pressure lines set to zero at the external auditory  
32  
33 meatus.  
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38 After catheter placement and burr hole craniotomy, the first blood samples for blood gas  
39  
40 analysis using a standard blood gas oximetry system (ABL 735, Radiometer, Copenhagen,  
41  
42 Denmark) were collected into heparinised syringes. In each sample, pH,  $p_a\text{O}_2$ ,  $p_a\text{CO}_2$ , actual  
43  
44 base excess, actual bicarbonate, sodium, chloride, potassium, lactate, haemoglobin and  
45  
46 haematocrit were measured. Additionally, a further blood sample was drawn to measure  
47  
48 serum phosphate ( $\text{PO}_4$ ), serum albumin and serum osmolality using standard laboratory  
49  
50 techniques. The piglets were then randomly assigned to receive either  $100\text{ml}\cdot\text{kg}^{-1}$  NS-G1  
51  
52 (Table 1, Central Pharmacy Department, Hanover Medical School, Hanover, Germany) or  
53  
54  $100\text{ml}\cdot\text{kg}^{-1}$  BS-G1 (Table 1, E148 G1 PÄD, Serumwerk Bernburg, Bernburg, Germany),  
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56 within one hour. During fluid administration, blood samples were collected every 15 minutes.  
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3 When the infusion was stopped, the last blood sample was collected and the piglets were  
4  
5 euthanized by intravenous injection of pentobarbital.  
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7

8 For calculation of strong ion difference (SID), the sum of chloride and lactate concentrations  
9  
10 was subtracted from the sum of sodium and potassium concentrations. The total of weak acids  
11  
12 ( $A^-$ ) was calculated using the equation of Fencl *et al.*(8)  
13

$$14 \quad [A^-] = [\text{albumin } [g\cdot l^{-1}] \cdot (0.123 \cdot \text{pH} - 0.631)] + [\text{phosphate } [mmol\cdot l^{-1}] \cdot (0.309 \cdot \text{pH} - 0.469)]$$

15  
16  
17 The power calculation was carried out using the nQuery Advisor software 6.0 (Statistical  
18 solutions, Cork, Ireland) with a power of 90% and a significance level ( $\alpha$ ) of 0.05. This  
19  
20 showed that a sample size of 5 piglets per group would allow detection of a difference of 10%  
21  
22 in the sodium, chloride and osmolality values in each infusion group. As all measured and  
23  
24 calculated data described above were normally distributed (as tested by Kolmogorov-Smirnov  
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26 tests), these are presented as mean values with standard deviations. For demographic data and  
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28 measured values before and after fluid administration two-way ANOVA test were performed.  
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Significance was accepted at  $p < 0.05$ . Recorded data were analysed using the SPSS 15.0  
software for Windows (SPSS Software, Munich, Germany).

## Results

41 All ten piglets used in the study received their intended treatment, completed the study  
42  
43 protocol and were analysed as reported. The two groups were comparable for weight (BS-G1  
44  
45 group  $11.7 \pm 2.0\text{kg}$ , NS-G1 group  $11.9 \pm 1.6\text{kg}$ ) and length (BS-G1 group  $73.4 \pm 3.5\text{cm}$ , NS-  
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47 G1 group  $73.5 \pm 3.5\text{cm}$ ). At baseline, there were no between-group differences in acid-base  
48  
49 variables, concentrations of serum electrolytes, albumin and glucose, serum osmolality,  
50  
51 haemoglobin, haematocrit, CVP or ICP (Tables 2 and 3). However, mean arterial pressure  
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53 differed significantly between the groups at the start of the study, with the higher values in the  
54  
55 NS-G1 group. During the experiment, haemoglobin, haematocrit, albumin and phosphate  
56  
57 decreased and CVP increased significantly in both groups, while the mean arterial pressure  
58  
59 remained almost stable, preserving the primarily significant between-group difference (Table  
60

1  
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3 2). ICP increased significantly in both groups, but remained within physiological ranges  
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5 (Table 2). The increase in chloride concentrations was significantly higher in the NS-G1  
6  
7 group. Actual bicarbonate and actual base excess decreased in both groups and were  
8  
9 significantly lower in the NS-G1 group at study end (Figure 1, Table 3). Regarding further  
10  
11 acid-base variables, significant decreases in SID and  $A^-$  were found in both groups.  
12  
13 Osmolality and glucose concentrations increased with both BS-G1 and NS-G1 infusion.  
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15 Sodium levels in the NS-G1 group increased significantly, while the potassium and lactate  
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17 concentrations decreased at the same time. The infusion of balanced electrolyte solution  
18  
19 caused no significant changes in sodium, potassium and lactate levels.  
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## 27 Discussion

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29 The objective of this prospective animal study was to determine the margin of safety of a  
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31 novel isotonic balanced electrolyte solution (BS-G1) in comparison to the likewise  
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33 recommended isotonic normal saline solution (NS-G1) both with 1% glucose. The  
34  
35 experimental study design was chosen to illustrate an accidental hyperhydration. Key findings  
36  
37 were mild hyperchloraemic acidosis after administration of NS-G1 and stable acid-base  
38  
39 parameters after BS-G1 application. The development of moderate hyperglycaemia resulting  
40  
41 in increased serum osmolality in both groups, while the intracranial pressures remained stable  
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43 within the physiological range.  
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48 Intravenous fluid administration influences the composition of serum electrolytes, osmolality,  
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50 acid-base balance and glucose concentration due to the composition of the administered fluid.  
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53 Incidents due to parenteral infusion in infants and children are mainly caused by changes in  
54  
55 one of these parameters (3, 9-11). In case of a high volume load, these effects are more  
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57 pronounced and may include fatal complications, as reported in several case reports (3).  
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60 A balanced volume replacement strategy is a well established concept for perioperative fluid  
management using plasma adapted isotonic crystalloid solutions with a physiological



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3 electrolyte pattern and acetate as bicarbonate precursor in order to prevent iatrogenic acid-  
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5 base imbalances (12, 13). Acetate may be preferable to lactate because it is metabolised  
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7 significantly faster, more independently of hepatic function, with a lower increase in oxygen  
8  
9 consumption and no interference with the diagnostic use of lactate as a marker of low tissue  
10  
11 perfusion (14, 15). Rapid administration of high acetate doses (e.g. during haemodialysis)  
12  
13 may lead to metabolic disturbances like a transient elevated blood glucose level or the release  
14  
15 of cytokines (16) with a potential decrease in mean arterial pressure. However, in our study  
16  
17 blood glucose levels increased comparable in both groups and mean arterial blood pressures  
18  
19 and acid-base- electrolyte parameters were stable during hyperhydration with the acetate  
20  
21 containing BS-G1 solution.  
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26  
27 When compared to extracellular fluid or plasma normal saline contains unphysiological large  
28  
29 amounts of sodium ( $154 \text{ mmol l}^{-1}$ ) and chloride ( $154 \text{ mmol l}^{-1}$ ). The potential acidifying effect  
30  
31 of large volumes of normal saline solutions on plasma has been recognised in several  
32  
33 controlled trials (17, 18), but controversy has surrounded the aetiology of this phenomenon. In  
34  
35 traditional terms, according to Hendersson-Hasselbalch, acidosis from fluid administration  
36  
37 implies that plasma expansion and the consecutive dilutional reduction of plasma bicarbonate  
38  
39 are the underlying mechanisms (19). Based on these findings, we demonstrated a decrease in  
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41 actual bicarbonate and mild hyperchloraemic acidosis with normal saline infusion and almost  
42  
43 stable acid-base conditions after BS-G1 application.  
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48  
49 In contrast to Hendersson-Hasselbalch, the Stewart approach, which is discussed in detail  
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51 elsewhere (20), defines  $p_a\text{CO}_2$ , SID and the sum of all anionic charges of weak plasma acids  
52  
53 (mainly albumin and phosphate) as independent pH-regulating variables, whereas pH and  
54  
55 bicarbonate are dependent variables (21). Assuming a constant  $p_a\text{CO}_2$ , the Stewart approach  
56  
57 provides an alternative to simple dilution as an explanation for acidosis and postulates that a  
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59 decrease in SID or an increase in  $A^-$  will result in a decrease in pH, or vice versa an increase  
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in SID or a fall in  $A^-$  will cause a pH increase (21). Morgan *et al.* (22) previously

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2  
3 demonstrated a linear relationship between crystalloid SID and post-dilutional metabolic acid-  
4 base status. They proved that a crystalloid infusion with a SID of  $24 \text{ mmol l}^{-1}$  preserves  
5 base status. They proved that a crystalloid infusion with a SID of  $24 \text{ mmol l}^{-1}$  preserves  
6 normal acid-base status (22). According to these findings, in the present study the change in  
7  
8 SID was significantly lower in the group with the novel isotonic balanced electrolyte solution  
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10 (chloride  $118 \text{ mmol l}^{-1}$ , SID  $26 \text{ mmol l}^{-1}$ ) when compared to normal saline (chloride  $154$   
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12  $\text{mmol l}^{-1}$ , SID  $0 \text{ mmol l}^{-1}$ ). The simultaneous decreases in  $A^-$ , caused by the dilution of serum  
13  
14 albumin, prevent severe metabolic acidosis (22). In other words, according to Stewart, the  
15  
16 hyperchloraemic acidosis in both groups is completely (BS-G1 group) or mostly (NS-G1  
17  
18 group) neutralised by hypoalbuminaemic alkalosis.  
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24 The choice of glucose concentration in perioperative solutions in paediatric anaesthesia is a  
25  
26 compromise between avoiding hypoglycaemia and hyperglycaemia (23). Several clinical  
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28 trials comparing the perioperative use of infusion solutions containing no glucose, 1% glucose  
29  
30 or 5% glucose showed that the use of 1% glucose prevents hypoglycaemia and lipid  
31  
32 mobilisation and is associated with blood glucose concentrations in the normal range (24, 25).  
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34 The present study showed that in the case of accidental hyperhydration 1% glucose  
35  
36 concentration may lead to moderate hyperglycaemia (study end: BS-G1  $12.6 \pm 1.8 \text{ mmol l}^{-1}$ ,  
37  
38 NS-G1  $13.0 \pm 2.0 \text{ mmol l}^{-1}$ ) but the plasma glucose concentrations did not reach levels where  
39  
40 severe health threatening events were likely. Actually, in a recent study of de Ferranti *et al.*  
41  
42 (26), evaluating long- term neurological development of neonates and infants after correction  
43  
44 of transposition of the great arteries, patients who presented low blood glucose concentrations  
45  
46 had an increased risk of electroencephalic seizures whereas high glucose concentrations were  
47  
48 not associated with worse neurodevelopmental outcomes.  
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53 However, rapid infusion with normal saline and balanced electrolyte solution with 1% glucose  
54  
55 leads to a significant increase of serum osmolality. Serum osmolality is primarily determined  
56  
57 by sodium, glucose and urea concentrations. Urea concentrations were not measured in this  
58  
59 study setting, but hyperhydration with urea-free solutions makes stable to decreased urea  
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3 concentrations likely. The simultaneous decrease (BS-G1 group) or only modest increase in  
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5 sodium concentrations (NS-G1 group) suggests that the increase in glucose concentrations is  
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7 the main reason for the rise in serum osmolality in both groups. In any case, serum osmolality  
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9 remained within the physiological range; therefore, severe effects on the osmotic balance did  
10  
11 not occur. The significant increase of central venous pressure (CVP) in both groups, was most  
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13 likely due to the volume load and may contribute to the likewise moderate increase in ICP.  
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15 Nevertheless, although the increases in CVP and ICP were statistically significant, the values  
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17 remained in physiological ranges, so that the clinical impact is negligible.  
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22 In conclusion, both solutions showed a wide margin of safety in the case of accidental  
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24 hyperhydration with less acid-base-electrolyte changes when using the novel isotonic  
25  
26 balanced electrolyte solution. The addition of 1% glucose led to moderate hyperglycaemia  
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28 with a concomitant increase in serum osmolality in both groups, while CVP and ICP remained  
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30 in physiological ranges. Therefore, this novel solution can be regarded, even in the case of  
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32 accidental hyperhydration, as being almost `foolproofed` (6) and should enhance patients  
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34 safety.  
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13 Cardiac Surgery Is Not Associated with Adverse Neurodevelopmental Outcomes at 1,4, and 8  
14 Years. *Anesthesiology* 2004; **100**: 1345-1352.  
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**Table 1**

	Serum at baseline (n=10)	BS-G1	NS-G1
Sodium (mmol·l <sup>-1</sup> )	136.6 ± 3.1	140.0	154.0
Potassium (mmol·l <sup>-1</sup> )	3.7 ± 0.3	4.0	-
Calcium (mmol·l <sup>-1</sup> )	1.4 ± 0.1	2.0	-
Chloride (mmol·l <sup>-1</sup> )	102.2 ± 2.3	118.0	154.0
Actual bicarbonate (mmol·l <sup>-1</sup> )	26.5 ± 1.3	-	-
Acetate (mmol·l <sup>-1</sup> )	-	30.0	-
Lactate (mmol·l <sup>-1</sup> )	1.1 ± 0.4	-	-
Glucose (mmol·l <sup>-1</sup> )	3.4 ± 0.9	55.0	55.0

**Table 2**

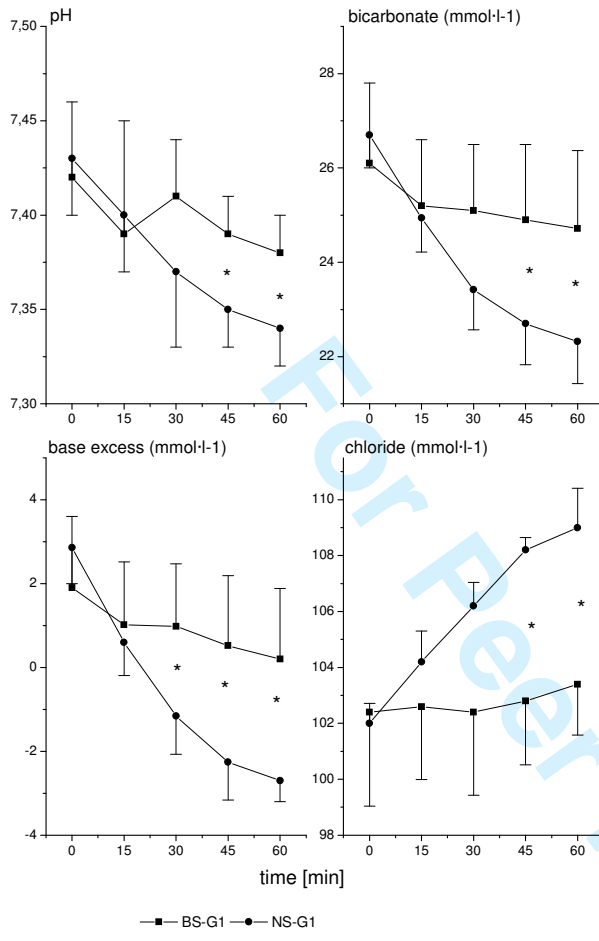
Variable	Baseline		<sup>1</sup> p	Study end		<sup>2</sup> p
	BS-G1	NS-G1		BS-G1	NS-G1	
Haemoglobin (g·dl <sup>-1</sup> )	8.7 ± 0.3	9.2 ± 0.7	ns	6.6 ± 0.1*	7.0 ± 0.7*	ns
Haematocrit (%)	27.2 ± 0.8	28.4 ± 2.0	ns	20.7 ± 0.4*	22.0 ± 2.0*	ns
Mean arterial pressure (mmHg)	71.8 ± 3.3	88.2 ± 7.5	<0.05	75.6 ± 1.1	94.0 ± 13.7	<0.05
Central venous pressure (mmHg)	4.2 ± 2.1	5.0 ± 2.2	ns	12.4 ± 2.0*	10.4 ± 3.1*	ns
Intracranial pressure (mmHg)	4.2 ± 1.8	5.4 ± 6.1	ns	8.0 ± 2.0*	8.8 ± 6.3*	ns

**Table 3**

Variable	Baseline			Study end		
	BS-G1	NS-G1	<sup>1</sup> p	BS-G1	NS-G1	<sup>2</sup> p
pH	7.42 ± 0.0	7.43 ± 0.0	ns	7.38 ± 0.0	7.34 ± 0.0*	<0.05
p <sub>a</sub> CO <sub>2</sub> (mmHg)	41.6 ± 5.0	41.6 ± 4.0	ns	42.6 ± 2.6	42.9 ± 3.9	ns
Actual base excess (mmol·l <sup>-1</sup> )	1.9 ± 1.7	2.9 ± 0.9	ns	0.2 ± 1.7*	-2.7 ± 0.5*	<0.05
Osmolality (mosmol·kg <sup>-1</sup> )	289.4 ± 5.4	291.6 ± 3.7	ns	299.2 ± 4.9*	303.2 ± 6.2*	ns
Glucose (mmol·l <sup>-1</sup> )	3.4 ± 1.3	3.4 ± 0.5	ns	12.6 ± 1.8*	13.0 ± 2.0*	ns
Sodium (mmol·l <sup>-1</sup> )	136.8 ± 4.2	136.4 ± 2.1	ns	135.4 ± 2.8	138.8 ± 2.1*	ns
Potassium (mmol·l <sup>-1</sup> )	3.7 ± 0.3	3.8 ± 0.4	ns	3.4 ± 0.2	3.1 ± 0.3*	ns
Chloride (mmol·l <sup>-1</sup> )	102.4 ± 3.4	102.0 ± 0.7	ns	103.4 ± 1.8	109.0 ± 1.4*	<0.05
Actual bicarbonate (mmol·l <sup>-1</sup> )	26.1 ± 1.7	26.9 ± 0.7	ns	24.7 ± 1.7*	22.3 ± 0.9*	<0.05
Lactate (mmol·l <sup>-1</sup> )	1.1 ± 0.5	1.0 ± 0.2	ns	1.3 ± 0.2	0.8 ± 0.2*	<0.05
Phosphate (mmol·l <sup>-1</sup> )	2.5 ± 0.6	2.4 ± 0.7	ns	2.0 ± 0.5*	1.98 ± 0.46*	ns
Albumin (g·l <sup>-1</sup> )	27.3 ± 2.8	28.0 ± 0.9	ns	19.1 ± 2.4*	19.2 ± 0.8*	ns
Strong ion difference (mmol·l <sup>-1</sup> )	37.0 ± 3.0	37.1 ± 1.9	ns	34.1 ± 2.5*	32.1 ± 1.6*	ns
Weak acids (mmol·l <sup>-1</sup> )	12.3 ± 1.8	12.3 ± 1.5	ns	8.9 ± 2.0*	8.7 ± 1.0*	ns



Figure 1



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3 **Table 1** Composition of piglets' serum at baseline (expressed as means  $\pm$  SD), balanced  
4 electrolyte solution with 1% glucose (BS-G1) and normal saline with 1% glucose (NS-G1).  
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10 **Table 2** Comparison of haemoglobin, haematocrit, mean arterial pressure, central venous  
11 pressure and intracranial pressure at baseline and at the end of the study after infusion of  
12 100 ml·kg<sup>-1</sup> of either balanced electrolyte solution with 1% glucose (BS-G1) or normal saline  
13 with 1% glucose (NS-G1), within one hour.  
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20 Data are expressed as means  $\pm$  SD, <sup>1</sup>p value at baseline, BS-G1 vs. NS-G1, <sup>2</sup>p value at end of  
21 study, BS-G1 vs. NS-G1, \* p<0.05, end of study vs. baseline  
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28 **Table 3** Comparison of acid-base, electrolyte parameters, osmolality, glucose and albumin at  
29 baseline and at the end of the study after infusion of 100 ml·kg<sup>-1</sup> of either balanced electrolyte  
30 solution with 1% glucose (BS-G1) or normal saline with 1% glucose (NS-G1), within one  
31 hour.  
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38 Data are expressed as means  $\pm$  SD, <sup>1</sup>p value at baseline, BS-G1 vs. NS-G1, <sup>2</sup>p value at end of  
39 study, BS-G1 vs. NS-G1, \* p<0.05, end of study vs. baseline  
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47 **Figure 1** Changes in pH, bicarbonate, base excess and chloride concentrations after infusion  
48 of 100ml·kg<sup>-1</sup> of either balanced electrolyte solution with 1% glucose (BS-G1) or normal  
49 saline with 1% glucose (NS-G1), within one hour.  
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55 Data are expressed as means  $\pm$  SD, \* p<0.05, BS-G1 vs. NS-G1  
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